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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/260,037	03/02/1999	ORON YACOBY-ZEEVI	910/13	6023

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	**PAPER NUMBER**
1652	22

DATE MAILED: 12/28/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/260,037	YACOBY-ZEEVI, ORON	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-57 and 59-70* is/are pending in the application.

4a) Of the above claim(s) *60-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *54-57 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 21 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after **non-final rejection.** This application is not eligible for continued examination under 37 CFR 1.114. Applicants attention is drawn to the M.P.E.P:

> **37 CFR 1.114. Request for continued examination.**
> (a) If prosecution in an application is **closed**, an applicant may request continued examination of the application by filing a submission and the fee set forth in § 1.17(e) prior to the earliest of:
> (1) Payment of the issue fee, unless a petition under § 1.313 is granted;
> (2) Abandonment of the application; or
> (3) The filing of a notice of appeal to the U.S. Court of Appeals for the Federal Circuit under 35 U.S.C. 141, or the commencement of a civil action under 35 U.S.C. 145 or 146, unless the appeal or civil action is terminated.
> (b) Prosecution in an application is closed as used in this section means that the application is under appeal, or that the last Office action is a final action (§ 1.113), a notice of allowance (§ 1.311), or an action that otherwise closes prosecution in the application.
> (c) A submission as used in this section includes, but is not limited to, an information disclosure statement, an amendment to the written description, claims, or drawings, new arguments, or new evidence in support of patentability. If reply to an Office action under 35 U.S.C. 132 is outstanding, the submission must meet the reply requirements of § 1.111.
> (d) If an applicant timely files a submission and fee set forth in § 1.17(e), the Office will withdraw the finality of any Office action and the submission will be entered and considered. If an applicant files a request for continued examination under this section after appeal, but prior to a decision on the appeal, it will be treated as a request to withdraw the appeal and to reopen prosecution of the application before the examiner. An appeal brief under § 1.192 or a reply brief under § 1.193(b), or related papers, will not be considered a submission under this section.

Since prosecution in this application was not previously closed, this request for reexamination was improper.

Applicants addition of new claims 60-70 is acknowledged, in Paper No:19, 10/9/2001. As these newly added claims

Newly submitted claims 60-70 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Newly added claims 60-66 would be grouped with originally restricted Group III, and claims 67-70 would properly be grouped with original Group IV and are distinct for the reasons previously given in Paper No: 2, 10/6/1999.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 60-70 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants acknowledge that claims 54-57 and 59-70 are present in the application.

Claims 60-70 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-57 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-57 and 59 are indefinite in the recitation of "a purified, natural or recombinant, glycosaminoglycan degrading enzyme" in that it is unclear if applicants intent is to a "purified natural or purified recombinant glycosaminoglycan degrading enzyme" or to a "a purified, natural, or recombinant glycosaminoglycan degrading enzyme". For the purpose of examination, the recitation has been interpreted as the second, broader of the two interpretations, "a purified, natural, or recombinant glycosaminoglycan degrading enzyme".

Claims 54-57 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a biological preparation comprising ex vivo, cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and a natural or recombinant purified heparanase being externally adhered thereto, does not reasonably provide enablement for a biological preparation comprising ex vivo, a cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and any natural or recombinant purified glycosaminoglycan degrading enzyme being externally adhered thereto. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 54-57 and 59 are so broad as to encompass a biological preparation comprising ex vivo, a cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and any natural or recombinant

purified glycosaminoglycan degrading enzyme being externally adhered thereto. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glycosaminoglycan degrading enzymes broadly encompassed by the claims. Since the specific functional properties of the glycosaminoglycan degrading enzyme adhered to said cells or tissue determines the effectiveness of utility of said biological preparation, predictability of those enzymes that may be adhered to said cells or tissue and result in the desired activity requires a detailed knowledge of said glycosaminoglycan degrading enzymes and how the specific enzyme used relates to intended biological function of the preparation. However, in this case the disclosure is limited to a biological preparation comprising ex vivo, cells in suspension or a tissue selected from the group consisting of an embryo, a skin graft and a nerve, and any natural or recombinant purified heparanase enzyme being externally adhered thereto.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the utility of the biological preparation comprising ex vivo, any cells in suspension or a tissue portion and any natural or recombinant purified glycosaminoglycan degrading enzyme being externally adhered thereto, encompassed by the claims. It would require undue experimentation of the skilled artisan to use any of the claimed biological preparation comprising ex vivo, any natural or recombinant purified glycosaminoglycan degrading enzyme being externally adhered thereto. The specification is limited to teaching use of the glycosaminoglycan degrading enzyme, heparanase and provides no guidance with regard to other glycosaminoglycan degrading enzymes which may also be used. In view of the great breadth of the claims, amount of experimentation required to make the claimed biological preparation, the lack of guidance, working examples, and unpredictability of the art in predicting which

glycosaminoglycan degrading enzymes would be useful, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the biological preparations encompassed by this claim.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any biological preparation comprising ex vivo, any cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and any purified, natural or recombinant, glycosaminoglycan degrading enzyme being externally adhered thereto. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartlett et al.

Bartlett et al. teach a comparative analysis of the ability of leucocytes, endothelial cells and platlets to degrade the subendothelial basement membrane. Bartlett et al. specifically teach preparation of human platlets from venous blood and resuspended in

RPMI-1640 medium containing 10% FCS. Bartlett et al. further teach that both platlets and endothelial cells in suspension expressed heparanase and each of these cell suspensions were able to degrade the extracellular matrix in an extracellular matrix assay, thus these enzymes are adhered to these cells such that they are able to degrade this extracelluar matrix. Further, Bartlett et al. teach that expression of such enzymes is necessary for the adhesion, extravasation and movement of these cells through the blood vessel wall prior to entry into inflammatory sites. Applicant is reminded that as discussed in previous office actions, applicants amendment of claims to recite "for use in vivo" and "so as to enhance extravasation... of said cells in vivo", are intended "uses" of the biological preparation therefore carry no patentable weight.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuks et al. (US Pat No: 5,362,641), Wang et al. (J. Orthop. Res., 14 (2): 149-153 1996, abstract) and Myers et al. (Am J. Surg. 170(1): 75-83, 1995 Jul).

Fuks et al. teach a substantially purified heparanase from human SK-HEP-1 cell line and a method to purify the heparanase. They teach the use of this heparanase as the basis for a pharmaceutical composition comprising the heparanase in combination with a pharmaceutically acceptable, preferably slow releasing carrier (column 5, lines 17-30). Such a composition is useful for the treatment of wounds and enhancement of the wound-healing process. Fuks et al. further teach that the extracellular matrix

appears to be essential to the control of cell proliferation and morphogenesis and that heparan sulfate proteoglycans (HSPG), as a principal component of basement membranes plays a integral role in tissue architecture and function. A number of normal and abnormal physiological conditions and disorders are associated with the degradation of the extracellular matrix of various tissues, such as neutrophil mobilization during the inflammatory process as well as tumor cell invasion during metastasis. Thus the invading cells must be capable of producing ECM degrading enzymes in order to move through the tissue. The enzymes include in addition to heparanase, chrondroitinase, hyaluronidase and keratanase as well as other ECM degrading enzymes.

Fuks et al. teach in addition to the above function ECM degradation an additional function of heparanase is the release of growth factors from basement membranes and subendothelial ECM such as angiogenic, endothelial (ECGF) and fibroblast growth factors (FGF). FGF is essential in the proliferation of fibroblasts and virtually all other mesoderm and neuro-ectoderm-derived cells which are responsible for the production of collagen tissue. Fuks et al. teach that FGF is stored within the basement membrane and bound to heparan sulfate until an exogenous factor such as heparanase causes its release. Fuks et al. teach that heparanase may provide an effective method to mobilize and activate the ECM-bound FGF and hence promote the wound healing process as well as other pathological conditions which are likely to benefit from neovascularization promoted by FGF including cardiac, cerebral and peripheral ischaemic diseases associated with vascular damage. Other potential clinical applications for angiogenic factors taught by Fuks et al. are in processes such as ovulation, hair growth, transplantation, nerve regeneration and bone and cartilage repair.

Wang et al. teach that basic fibroblast growth factor enhances bone-graft incorporation. Specifically Wang et al. teach the implantation of bone grafts, which had been previously soaked overnight in basic fibroblast growth factor, into the proximal tibiae of recipient rats.

Myers et al. teach the transplantation of keratinocytes in the treatment of wounds.

Myers et al. teach that keratinocyte grafting can be used to treat acute traumatic and chronic non-healing wounds and the keratinocyte sheets secrete many growth factors which have effects on wound healing apart from the "take" of the keratinocyte sheet. Myers et al. show that pretreatment of the wound bed with viable dermis greatly increases the take of keratinocyte grafts.

One of ordinary skill in the art at the time of filing would have been motivated to pretreat keratinocyte grafts prior to implantation of the grafts in recipient tissue with a growth factor or other factor to stimulate integration of the graft into the recipient tissue. Such pretreatment of tissue prior to its transplantation is taught by Wang et al. Based on the teaching of Fuks et al. one of ordinary skill in the art at the time of filing would have been motivated to treat said keratinocyte grafts with heparanase as opposed to a specific growth factor in order to stimulate the release of endogenous growth factors such as FGF from the recipient tissue. As taught by Fuks et al., the use of heparanase to release FGF from its natural setting has the advantage of the cells responding locally to the endogenous natural growth factors and appropriate amount as opposed to high doses of FGF which have been shown to be toxic to various cell types including endothelial cells. Further Fuks et al. teach that heparanase has other beneficial effects on the wound healing process such as the breakdown of the ECM, a necessary part of the integration of invading or transplanted cells.

Therefore, claims 57 and 59 are made obvious by Fuks et al., Wang et al. and Myers et al.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
December 14, 2001

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800
1600